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SYNTHESIS OF TRISULFANILYLMELAMINE

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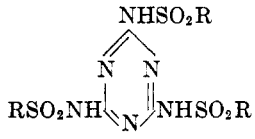
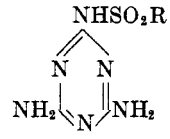
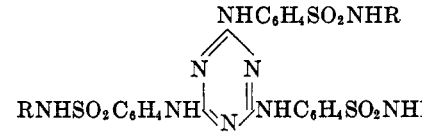
A number of reactions which yield trisulfonylmelamines (I) have recently been described (1–3). In view of the cytotoxic properties of certain substituted triazines (4), and the close structural relationship between the powerful bacteriostatic compounds sulfapyridine or sulfadiazine with trisulfanilylmelamine, this new sulfonyltriazine (I, R = p-$NH_2C_6H_4$•) has now been prepared for chemotherapeutic evaluation. Amongst related structures, monosulfanilylmelamine (II) has previously been described (5), as have substituted p-sulfonamidotriarylmelamines (III) (6).



I



II



III

Two of the synthetic routes previously developed in this laboratory (2, 3) were successfully applied to the preparation of tri(p-acetaminobenzenesulfonyl)-melamine (I, R = p-CH_3CONH•C_6H_4•). The compound was obtained in moderate yields when p-acetaminobenzenesulphonyldicyandiamide was treated with an excess of p-acetaminobenzenesulfonyl chloride in pyridine. In this reaction, the trisulfonylmelamine may arise from the primarily formed N-cyano-N,N′-disulfonylguanidine IV (*i.e.* a disulfonyldicyandiamide). The breakdown of some of this dimeric intermediate into the monomeric sulfonylcyanamide (V) would provide the units from which the trimeric product (I) is formed (equations 1–3).

$$RSO_2NHC(:NH)NHCN + RSO_2Cl \rightarrow RSO_2NHC(:NH)N(SO_2R)CN\ (IV) + HCl \quad 1.$$

$$RSO_2NHC(:NH)N(SO_2R)CN \rightarrow 2\ RSO_2NHCN\ (V) \quad 2.$$

$$RSO_2NHC(:NH)N(SO_2R)CN + RSO_2NHCN \longrightarrow I \quad 3.$$
$$3\ RSO_2NHCN \longrightarrow$$

Superior yields of the desired product were obtained more conveniently by the condensation, in high-boiling inert media, of cyanuric chloride and sodium p-acetaminobenzenesulfonamide in the molar proportion 1:6 (equation 4). Since the resulting trisulfonylmelamine (I) is a stronger acid than the sulfonamide from which it is derived, it was formed as the trisodium salt: two moles of sodium sulfonamide are therefore required for the replacement of one atom of chlorine in the triazine nucleus (compare, 7).

$$(CNCl)_3 + 6\ RSO_2NNaH \rightarrow (I;\ \text{trisodium derivative}) + 3\ RSO_2NH_2 + 3\ NaCl \quad 4.$$

Boiling alkali converted the triacetyl derivative smoothly into trisulfanilylmelamine. This was readily benzoylated, or re-acetylated to the starting material, showing the absence of rearrangement during the hydrolysis. Trisulfanilyl-

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

Compound	λ_{min}	log ϵ	λ_{max}I	log ϵ	λ_{min}	log ϵ	λ_{max}II	log ϵ	Ref
I, R = C_6H_5•	—	—	230	4.69	262	3.84	273	3.97	3
I, R = o-$CH_3C_6H_4$•	221	4.55	231.5	4.60	259	4.00	272	4.19	3
I, R = p-$CH_3C_6H_4$•	221.5	4.53	236	4.70	262*	3.90	—		3
I, R = p-$CH_3CONHC_6H_4$•	236	4.40	267	4.85	—		—		†
I, R = p-$NH_2C_6H_4$•	237	4.15	279	4.70	—		—		†
Sulfanilylbenzamidine	236	4.62	260	4.75	—		—		8
2-(Sulfanilyl)-4,6-dimethyl-1,3-diazine	243	3.70	272	4.17	—		—		9

* Inflection † Present work.

melamine resisted the hydrolytic action of alkalis, but its structure was further confirmed by fission with ethanolic hydrogen chloride when appropriate yields of cyanuric acid and sulfanilamide were obtained.

An examination of the ultraviolet absorption spectra of trisulfanilylmelamine and its triacetyl derivative confirms our previous conclusion (3) that the absorption curves of trisulfonylmelamines are characteristic of the substituents rather than the triazine nucleus. As expected, the spectrum of trisulfanilylmelamine was similar to those of structurally related sulfonamides, but different from those of other members of the triarylsulfonylmelamine series (Table I).

Trisulfanilylmelamine, in the form of its trisodium salt, displays bacteriostatic properties against streptococci and pneumococci *in vitro*, being more powerful against the latter group than sulphacetamide. Thus, in a typical series of tests, the compound was active against 8 out of 37 strains of pathogenic streptococci, and against 8 out of 10 strains of pneumococci. Toxicity tests on male mice show that the acute intravenous LD_{50} of the trisodium salt is 850 mg./kg.

EXPERIMENTAL[1]

Tri(p-acetaminobenzenesulfonyl)melamine. (a). From 1-(p-acetaminobenzenesulfonyl)-3-cyanoguanidine. A solution of 5.62 g. (0.02 mole) of this reactant [prepared according to Kaiser and Thurston (10)] in 40 ml. of anhydrous pyridine was treated, at room temperature, with 9.34 g. (0.04 mole) of *p*-acetaminobenzenesulfonyl chloride. The temperature of the solution rose to 55–60° and was kept in this range for 20 minutes. The reddish-orange liquid was slowly stirred into 300 ml. of ice-cold 1.5 *N* hydrochloric acid, and the resulting white precipitate was collected after several hours' storage. During the filtration, and particularly when allowed to air-dry (on a watch-glass), the product changed, first to a soft and later to a glass-like resinous orange substance. The dry powdered product (7–8.5 g.) was added to 150 ml. of boiling ethanol; as it dissolved a white solid began to separate so that complete solution was not observed. The resulting suspension was set aside for several days, and the separated solid was collected and washed with cold ethanol (ethanol filtrate: A). The crude product, melting at 285–295° (dec.) (yield, 4.05–5.1 g., 40–50%), was crystallized from 66% aqueous ethanol (80 ml. per g., recovery per crystallization, approx. 50%) and gave lustrous prisms of solvated tri(*p*-acetaminobenzenesulfonyl)mel-

[1] Melting points are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford, England.

amine, melting at 300–304° (dec., previously sintering at 290–295°). The compound is almost insoluble in the usual solvents, including acetic acid and nitrobenzene, but soluble in mixtures of ethanol and water. The material may be recovered from the mother liquors by the addition of benzene and distillation to a smaller volume. Light absorption:[2] $\lambda_{min.}^{alc.}$ 236 mμ; log ε, 4.4 $\lambda_{max.}^{alc.}$ 267 mμ; log ε, 4.85.

Anal. Calc'd for $C_{27}H_{27}N_9O_9S_3 \cdot C_2H_5OH$: C, 45.6; H, 4.3; N, 16.5; S, 12.6.
Found: C, 44.1; H, 4.5; N, 16.2; S, 12.3.

One hour's heating of the solvated product at 200–220° removed the ethanol of crystallization and gave tri(*p*-acetaminobenzenesulfonyl)melamine as an amorphous nearly white powder, melting at 302–304° (dec.).

Anal. Calc'd for $C_{27}H_{27}N_9O_9S_3$: C, 45.2; H, 3.8; N, 17.6.
Found: C, 44.7; H, 3.7; N, 18.1.

The ethanolic filtrates (A) contained a highly ethanol-soluble low-melting (60–90°) resinous material, which could be isolated by vacuum evaporation, and reprecipitation from its alkaline solution by hydrochloric acid. The yield of this material was 2–2.4 g. (21–25%, calculated as polymeric *p*-acetaminobenzenesulfonylcyanamide).

(b). *From cyanuric chloride.* A suspension of 16.5 g. (0.07 mole) of sodium *p*-acetaminobenzenesulfonamide [prepared in 85–92% yield from equivalent quantities of sodium ethoxide and *p*-acetaminobenzenesulfonamide in nearly boiling absolute ethanol] in 150 ml. of anhydrous freshly distilled boiling decahydronaphthalene containing 1.85 g. (0.01 mole) of cyanuric chloride, was refluxed with mechanical stirring during 2 hours. The resulting solid (17–18 g.) was collected after several hours' storage, dried, and dissolved in two or three successive portions of aqueous 0.2 *N* sodium hydroxide (total, 200–230 ml.) at room temperature. Acidification of the filtered cooled (0°) solution, to Congo Red, with 3 *N* hydrochloric acid precipitated the product, together with unchanged sulfonamide. The collected dried white solid (12–14 g.) was added to 180 ml. of boiling ethanol. Separation of the products, which set in while the solution was still hot, was completed by storage overnight; the whole mixture was then reheated to boiling, and the crude sulfonylmelamine was filtered off with suction (ethanol filtrates: B). After a further extraction with 30 ml. of boiling ethanol, the product showed a melting point of 295–302° (dec., previously sintering at 285°) (yield, 4.25–4.7 g., 56–62%). After being crystallized [see section (a) above], it consisted of solvated tri(*p*-acetaminobenzenesulfonyl)melamine and melted at 301–304° (dec., previously sintering at 292–295°); this melting point was undepressed by the admixture of material prepared by method (*a*).

Anal. Found: C, 44.3; H, 4.0; N, 16.3.

The excess of the *p*-acetaminobenzenesulfonamide employed was recoverable from the ethanolic filtrates B by evaporation to a small volume. The use of boiling anhydrous xylene as medium, thus lowering the reaction temperature from 190° to 140°, under the above conditions, or longer periods (up to 5 hours) reduced the yields to 15–30%.

Tri(p-aminobenzenesulfonyl)melamine. A solution of 7.63 g. (0.01 mole) of the above triacetyl derivative in 150 ml. of aqueous 1.5 *N* sodium hydroxide was refluxed during 4 hours, quickly filtered at the pump to remove traces of impurities, and the filtrate set aside at 0° for 12 hours. The separated trisodium salt of tri(*p*-aminobenzenesulfonyl)melamine was collected and rinsed with ice-water. The crude salt, obtained in 85–90% yields was readily purified, if required, by recrystallization from boiling water (10 ml. per g.; recovery per crystallization, 70–75%).

The crude trisodium salt was dissolved in 80 ml. of water at 80–90° and the solution slowly acidified (to litmus) with 15–18 ml. of 4 *N* acetic acid, while being simultaneously cooled externally by ice-water. The white precipitate was collected at 0°, washed with water, and dried; it melted at 220–222° (dec.) (yield, 4.15–4.7 g., 70–80%). Crystallization from boiling 50% ethanol (30 ml. per g., recovery per crystallization: 60–70%) afforded

[2] Ultraviolet absorption measurements were carried out with a Unicam S.P. 500 photoelectric spectrophotometer, absolute ethanol being used as solvent.

solvated tri(*p*-aminobenzenesulfonyl)melamine as lustrous platelets, melting at 215–218° (dec.). Light absorption: $\lambda_{min.}^{alc.}$ 237 mμ; log ε, 4.15; $\lambda_{max.}^{alc.}$ 279 mμ; log ε, 4.7.

Anal. Calc'd for $C_{21}H_{21}N_9O_6S_3 \cdot C_2H_5OH$: C, 43.3; H, 4.2; N, 19.8; S, 15.1.
Found: C, 43.4; H, 4.2; N, 19.9; S, 14.8.

Desolvolysis, by heating the above product, first at 180–190°, and later at 200° during 1 hour gave tri(*p*-aminobenzenesulfonyl)melamine, as an amorphous powder, melting at 221–223° (dec.).

Anal. Calc'd for $C_{21}H_{21}N_9O_6S_3$: C, 42.6; H, 3.55; N, 21.3; S, 16.2.
Found: C, 42.15, H, 3.6; N, 20.9; S, 15.7.

Acetylation of the product by acetic anhydride-pyridine (quantities and conditions, as described below for the tribenzoyl-derivative) gave 60% yields of the triacetyl-derivative, melting at 300–302° (dec., previously sintering at 285–295°). The melting point was undepressed in admixture with material prepared by method (*a*) and (*b*) (see above).

The trisilver salt of the compound was obtained as a white precipitate by the addition of a small excess of 10% aqueous silver nitrate to a hot 4% aqueous solution of the trisodium salt. It was collected at 0°, washed with water, and dried over phosphorus pentoxide.

Anal. Calc'd for $C_{21}H_{18}Ag_3N_9O_6S_3$: Ag, 35.5. Found (volumetrically, by thiocyanate): 35.6.

Tri(p-benzoylaminobenzenesulfonyl)melamine. A solution of 0.64 g. (0.001 mole) of tri(*p*-aminobenzenesulfonyl)melamine in 10 ml. of anhydrous pyridine, treated with 1.40 g. (0.01 mole) of benzoyl chloride, was kept on the steam-bath during 1 hour, and then stirred into 80 ml. of ice-cold 1.5 *N* hydrochloric acid. The collected precipitate was heated to 90° with two portions of 50 ml. of water (to remove the benzoic acid), collected, dried [yield of crude product, melting at 299–301° (dec.), 0.82 g.; 91%] and recrystallized from boiling nitrobenzene, when felted needles of the derivative, melting at 304–306° (dec.) were obtained. The substance is soluble in alkalis, but almost insoluble in the usual organic solvents.

Anal. Calc'd for $C_{42}H_{33}N_9O_9S_3$: C, 55.8; H, 3.65; N, 13.95.
Found: C, 55.2; H, 3.6; N, 14.3.

Hydrolysis of tri(p-aminobenzenesulfonyl)melamine. A solution of 0.96 g. (0.0015 mole) of this melamine in 500 ml. of absolute ethanol was refluxed, with passage of hydrogen chloride, during 30 hours. The evaporated solution (20 ml.) deposited cyanuric acid (yield, 0.125 g., 65%), which was identified by titration (11) and by its characteristic copper salt (12). Evaporation of the ethanolic filtrates to dryness gave the hydrochloride of sulfanilamide, which on dissolution in alkali, acidification with dilute hydrochloric acid, and crystallization from ethanol afforded needles of sulfanilamide (0.56 g., 72%), melting at 161–163°; the melting point was undepressed on admixture of authentic material.

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SUMMARY

Tri(*p*-aminobenzenesulfonyl)melamine has been synthesised by two methods, starting with cyanuric chloride or *p*-acetaminobenzenesulfonyldicyandiamide. The product displays bacteriostatic properties towards *streptococci* and *pneumococci in vitro*.

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